REMARKS

Introductory Comments

Claims 1-20 are pending. The Office has rejected all pending claims.

The Office has rejected claim 20 under 35 U.S.C. §101 for alleged non-statutory subject matter.

The Office has rejected claim 20 under 35 U.S.C. §112, second paragraph, for allegedly being indefinite.

The Office has rejected claims 1-4, 8, 9, 11, 12, and 14-20 under 35 U.S.C. §102(a), alleging that the claims are anticipated by U.S. Patent No. 5,900,238 to Gombotz *et al.*

The Office has rejected claims 1-20 under 35 U.S.C. §103(a), alleging that the claims were obvious over U.S. Patent No. 5,900,238, in view of Partidos *et al.* (1996) Immunology, and EP 0517565 to Callegaro *et al.*

These rejections are traversed and believed to be overcome for reasons discussed below.

Overview of the Amendments

Claim 1 has been amended to recite that the hyaluronic acid polymer is provided in the form of a microsphere. The amendment finds support throughout the specification, such as, for example, claim 8 as originally filed.

Claim 8 has been canceled.

Claims 9 and 10 have been amended to depend from claim 1 instead of the now canceled claim 8. The amendment thus corrects for dependency.

Claim 20 has been canceled.

Claims 21 and 22 have been added to recite that the micproshere is a nanosphere. The amendment finds support on page 19, lines 6-8 of the specification.

No new matter has been added by way of these amendments. Further, the amendments are made solely to expedite prosecution, for reasons unrelated to patentability, and do not constitute an acknowledgment that the Examiner's position is correct. Claims 1-7, 9-19 and 21-22 are now pending.

1. Rejection of Claim 20 under 35 U.S.C. §101

The rejection of claim 20 under 35 U.S.C. §101 is made moot by the cancellation of the claim.

2. Rejection of Claim 20 under 35 U.S.C. §112, Second Paragraph

The rejection of claim 20 under 35 U.S.C. §112, second paragraph, for allegedly being indefinite is made moot by the cancellation of the claim.

3. The Rejection of Claims 1-4, 8, 9, 11, 12, and 14-20 under 35 U.S.C. §102(a)

The Office has rejected claims 1-4, 8, 9, 11, 12, and 14-20 under 35 U.S.C. §102(a), alleging that the claims are anticipated by U.S. Patent No. 5,900,238 to Gombotz *et al.*

The applicants traverse the rejection. To anticipate a claim, a single source must contain all of the elements of the claim. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379, 231 USPQ 81, 90 (Fed. Cir. 1986). *Atlas Powder Co. v. E. I. du Pont De Nemours & Co.*, 750 F.2d 1569, 1574, 224 USPQ 409, 411 (Fed. Cir. 1984). Moreover, the single source must disclose all of the claimed elements "arranged as in the claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 9 USPQ 2d 1913, 1920 (Fed. Cir. 1989); *Connell v. Sears Roebuck & Co.*, 722 F.2d 1542, 1548, 220 USPQ 193, 198 (Fed. Cir. 1983). Finally, the law requires the reference be enabled so that the invention is taught and placed within the possession of the public. To be prior art under section 102 the reference must put the anticipating subject matter at issue into the possession of the public through an enabling disclosure. *Chester v. Miller*, 906 F.2d 1574, 1576 n.2, 15 U.S.P.Q.2d 1333, 1336 n.2 (Fed. Cir. 1990), citing *In re Donohue*, 766 F.2d 531, 533, 226 USPQ 619, 621 (Fed. Cir. 1985).

Gombotz *et al.* describe an alginate gel matrix. The alginate gel matrix is made by mixing a solution of alginate, a linear polysaccharide, and a solution of an antigen, and then spraying the mixture into a strontium nitrate solution, where the divalent cation crosslinks the alginate. The reference also provides a laundry list of possible alternative hydrogels that could be used instead of alginate. The alternative

hydrogels include cross-linked pectin, gelatin, collagen, albumin, chitosan, cellulose and its derivatives, hyaluronic acid and its ester derivatives, polyvinyl alcohol, polymethacrylic acid, starches and dextrans, polyvinyl pyrrolidone, pluronic polyols and polyethylene oxide. With so many alternative hydrogels to choose from, the reference does not provide an exact description of the invention claimed by the applicants. In addition, the enablement criteria cannot be met. Therefore, the reference cannot be used as the basis for a 102(a) rejection.

Case law makes clear that where a reference does not highlight a claimed mixture among the many dozen disclosed or suggested, the reference is not sufficient to anticipate claims reciting the specific combination. *In re Kollman* et al., 201 USPQ 193 (CCPA 1979). Furthermore, anticipation cannot be made out by hindsight selection based on an applicant's disclosure of variables of a broad generic disclosure. *In re Ruschig et al.*, 145 USPQ 274 (CCPA 1965). Thus, a generic formula that encompasses a large number of compounds does not describe and therefore anticipate, all of the compounds embraced by the generic teaching merely because they are within the scope of the formula. *In re Petering et al.*, 133 USPQ 275 (CCPA 1962). See, also, *Akzo N.V. v. U.S. Int'l Trade Commission*, 1 USPQ2d 1241, 1246 (Fed. Cir. 1986): (There is no anticipation if to arrive at the claimed invention one must randomly "pick and choose among a number of different polyamides, a plurality of solvents and a range of inherent viscosities.")

For example, in the only method disclosed by the reference for the encapsulation procedure, a mixture containing the polymer and the antigen is first prepared, and then the mixture is contacted with divalent cations to form the gel matrix. Without extensive and undue experimentation, it is not possible for one of skill in the art to determine which one of the alternative gels could form a matrix when exposed to the divalent cations. In addition, if one of the alternative polymers chosen did not form a matrix when exposed to a divalent cation, the reference does not teach or suggest how a matrix could be formed. For example, some of the other methods that could be used to prepare microparticles when using alternative hydrogels disclosed by the reference where divalent cations are not involved include precipitation with a supercritical antisolvent.

Various methods have been devised for precipitation with a supercritical antisolvent, including the semi-discontinuous method, and the continuous method. Thus, one of skill in the art would need to perform additional experiments that are nonroutine, and the reference, therefore, is not enabling for the multitude of additional hydrogels that could be used to form a microsphere.

Accordingly, since Gombotz *et al.* does not specifically call out or suggest applicant's particular combinations from the laundry list of possible polymers that could be used to make hydrogels, Gombotz *et al.* cannot anticipate the present claims. Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §102(a).

4. The Rejection of Claims 1-20 under 35 U.S.C. §103(a)

The Examiner has rejected claims 1-20 under 35 U.S.C. §103(a), alleging that the claims were obvious over U.S. Patent No. 5,900,238, in view of Partidos *et al.* (1996) Immunology, and EP 0517565 to Callegaro *et al.* The Examiner states that Gombotz *et al.* do not disclose claimed adjuvants or using influenza, but Partidos *et al.* teach LT-K63 as an effective mucosal adjuvant, and Callegaro *et al.* teach the use of hydaluronic ester microspheres for intranasal application of a protein.

The applicants traverse the rejection. In order to render claims obvious, the burden is on the Office to establish a *prima facie* case of obviousness for which three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations. The teachings or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Applicants submit that the cited references do not provide a reasonable expectation of success. Thus, a *prima facie* case of obviousness has not been presented by the Office.

The applicants have discussed the Gombotz *et al.* reference in detail above. The reference discloses a laundry list of additional hydrogels that could be used to form a

microsphere, and is not enabling for the specific combination claimed by the applicants. As the court stated in Beckman Instruments, Inc. v. LKB Produkter AB, 13 USPQ2d 1301 (Fed. Cir. 1989) "References relied upon to support a rejection for obviousness must provide an enabling disclosure. That is to say, they must place the claimed invention in the possession of the public." In another instance, the court stated "The test whether a particular compound described in the prior art may be relied upon to show obviousness is whether the prior art provided an enabling disclosure to the disclosed compound. Because the evidence showed that a certain compound was a "hypothetical structure," it was not persuasive of obviousness." Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 227 USPQ 657 (Fed. Cir. 1985). In the present case, the primary reference, Gombotz *et al.* is not an enabling disclosure for a composition comprising an hyaluronic acid ester polymer in the form of a microsphere and a selected antigen. Therefore, the Office has not presented a *primae facie* case of obviousness. In addition, due to the failure of the reference to provide an enabling disclosure, the references do not provide a reasonable expectation of success, and the rejection should be withdrawn.

Improper rejection

The applicants take this opportunity to bring to the attention of the Office that the rejection of independent claims 1 and 11 as anticipated by Gombotz *et al.* and then a separate rejection of the claims as obvious over Gombotz *et al.* in combination with either Partidos *et al.* or Callegaro *et al.*, where the secondary references are alleged to provide elements missing from Gombotz *et al.* is improper. For example, the Office states that Gombotz *et al.* do not disclose adjuvants or using influenza, but Partidos *et al.* teach LT-K63 as an effective mucosal adjuvant. The Office argues that it would have been obvious to use the specific adjuvant taught by Partidos *et al.* as the adjuvant suggested by Gombotz *et al.* with the expectation of enhancing the immunogenicity of the composition. If the primary reference was thought to contain all the elements of the applicants' invention, and therefore anticipatory, then combination with secondary references to provide missing elements would be unnecessary.

Independent claims 1 and 11 were rejected as anticipated by Gombotz *et al.* With respect to the same independent claims, the Office, in making the 103 rejection, points out the deficiencies in Gombotz *et al.* In the event the Office wanted to reject only the dependent claims as obvious over Gombotz *et al.* in view of Partidos *et al.* and Callegaro *et al.*, the applicants traverse the rejection. The independent claims are patentable over Gombotz *et al.*, therefore, the dependent claims, that contain all the elements of the independent claims, are also patentable over the cited art. The Office is respectfully requested to withdraw this rejection.

Supplemental IDS

The Office cited Partidos *et al.* (1996) Immunology 89: 483-487 in the Office Action under reply. The Office did not cite the reference in Form 892. The applicants therefore submit the reference in a supplemental IDS, and request that it be properly made of record.

CONCLUSION

Applicants respectfully submit that the claims comply with the requirements of 35 U.S.C. §§101, and 112 and define an invention that is patentable over the art. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

Please send all further written communications in this case to:

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APPENDIX A

Marked up Version of The Claims.

The claims were amended as follows:

1. (Amended) A composition comprising an hyaluronic acid ester polymer in the form of a microsphere and a selected antigen, wherein said antigen is present in an amount of approximately .1% to about 40% (w/w) antigen to hyaluronic acid polymer.

[8. (Cancel) The composition of claim 1, wherein the hyaluronic acid ester is provided in the form of a microsphere.]

9. (Amended) The composition of claim [8] 1, wherein the selected antigen is entrapped in the microsphere.

10. (Amended) The composition of claim [8] 1, wherein the selected antigen is adsorbed to the microsphere.

[20. (Cancel) Use of an hyaluronic acid ester polymer in the manufacture of a medicament for mucosal immunization, said medicament comprising said polymer and a selected antigen, wherein said antigen is present in an amount of approximately .1% to about 40% (w/w) antigen to hyaluronic acid polymer.]

--21. (New) The composition of claim 1, wherein the microsphere is a nanosphere.

22. (New) The composition of claim 11, wherein the microshphere is a nanosphere.--

APPENDIX B

Clean Copy of Claims Pending

1. (Amended) A composition comprising an hyaluronic acid ester polymer in the form of a microsphere and a selected antigen, wherein said antigen is present in an amount of approximately .1% to about 40% (w/w) antigen to hyaluronic acid polymer. .

2. The composition of claim 1, wherein said antigen is present in an amount of approximately 2% to about 25% (w/w) antigen to hyaluronic acid polymer.

3. The composition of claim 1, wherein the hyaluronic acid ester is selected from the group consisting of an hyaluronic acid where from about 75% to about 100% of free carboxyl groups are esterified with one or more alkyl groups, and a crosslinked derivative of hyaluronic acid in which about 0.5% to about 20% of the carboxyl groups of the hyaluronic acid polymer are crosslinked to hydroxyl groups of the same or a different hyaluronic acid molecule.

4. The composition of claim 1, further comprising an immunological adjuvant.

5. The composition of claim 4, wherein the adjuvant is a detoxified mutant of a bacterial ADP-ribosylating toxin selected from the group consisting of LT-K63 and LT-R72.

6. The composition of claim 1, wherein the selected antigen is a viral antigen.

7. The composition of claim 6, wherein the selected antigen is an influenza antigen.

9. The composition of claim 1, wherein the selected antigen is entrapped in the microsphere.

10. The composition of claim 1, wherein the selected antigen is adsorbed to the microsphere.

11. A composition comprising (a) a microsphere comprised of an hyaluronic acid ester polymer selected from the group consisting of an hyaluronic acid where from about 75% to about 100% of free carboxyl groups are esterified with one or more alkyl groups, and a crosslinked derivative of hyaluronic acid in which about 0.5% to about 20% of the carboxyl groups of the hyaluronic acid polymer are crosslinked to hydroxyl groups of the same or a different hyaluronic acid molecule; (b) a selected antigen entrapped in, or adsorbed to, the microsphere, wherein said antigen is present in an amount of approximately 2% to about 25% (w/w) antigen to hyaluronic acid polymer; and (c) an immunological adjuvant.

12. The composition of claim 11, wherein the selected antigen is entrapped in the microsphere.

13. The composition of claim 11, wherein the selected antigen is adsorbed to the microsphere.

14. A method of making a pharmaceutical composition which comprises combining the composition of claim 1 with a pharmaceutically acceptable mucosal excipient.

15. A method of making a pharmaceutical composition which comprises combining the composition of claim 11 with a pharmaceutically acceptable mucosal excipient.

16. A method of immunization which comprises mucosally administering a therapeutically effective amount of the pharmaceutical composition of claim 14 to a vertebrate subject.

17. A method of immunization which comprises mucosally administering a therapeutically effective amount of the pharmaceutical composition of claim 15 to a vertebrate subject.

18. The method of claim 16 wherein the administering is done intranasally.

19. The method of claim 17 wherein the administering is done intranasally.

21. (New) The composition of claim 1, wherein the microsphere is a nanosphere.

22. (New) The composition of claim 11, wherein the microshphere is a nanosphere.